Remarks

Reconsideration of this Application is respectfully requested.

Claims 84-122 and 127-131 are pending in the application, with claims 84 and 127 being the independent claims. Claims 84, 109, and 112 are sought to be amended. Support for the amendment to claim 84 is found, *inter alia*, at page 8, paragraphs [0019]-[0020] of the specification. Applicants point to paragraph [0019] of the Specification for what is meant by "traditional homologous recombination." Support for the amendments to claims 109 and 112 is found, *inter alia*, at page 67, paragraphs [0182] and [0183]. Because the Examiner as made the restriction requirement final, claims 123-126 have been canceled without prejudice. Applicants reserve the right to pursue the canceled subject matter in related applications. Claims 98, 100-102, and 104-106 have been withdrawn from consideration by the Examiner as reading solely on non-elected species, but remain pending. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112--Written Description

Claims 109 and 112 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed had possession of the claimed invention. (Office Action at

page 7, section 18.) According to the Examiner, "[t]his is a new matter rejection." *Id.* Applicants respectfully traverse this rejection.

The Examiner stated that he did not find support for the "'combination thereof' selection" of claims 109 and 112, which recite, "restriction site selected from the group consisting of NotI, ApaI, and a combination thereof." Applicants respectfully maintain that support for "combination thereof" is present in the specification. However, solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claims 109 and 112 to recite "one or more unique restriction sites," e.g., a unique NotI restriction site, a unique ApaI restriction site, or both a unique NotI and a unique ApaI restriction site. This amendment is for clarification, and is not believed to alter the scope of these claims. Support for the amendments to claims 109 and 112 is found, *inter alia*, at paragraphs [182] and [183] of the specification, and claims 109 and 112 as filed. Paragraph 182 states: "[i]n a *preferred* embodiment, a virus genome comprises a first recognition site for a first restriction endonuclease and a second recognition site for a second restriction endonuclease. . ." (emphasis added). Thus, paragraph 182 does not preclude there being just one unique restriction site. Paragraph 183 states: "In certain preferred vaccinia virus genomes, the first restriction enzyme is NotI, having the recognition site GCGGCCGC in the tk gene, and the second restriction enzyme is ApaI, having the recognition site GGGCCC in the tk gene." Therefore there is support for the recitation of "one or more unique restriction sites selected from the group consisting of a unique NotI restriction site, a unique ApaI restriction site, and a combination of a unique NotI restriction site and a unique ApaI restriction site." Applicants therefore respectfully request that the Examiner reconsider and withdraw this rejection.

Claims 84, 88-97, 99, 103, 107-122 and 127-131 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey that the inventors had possession of the claimed invention at the time the application was filed. (Office Action at page 7, section 18.) Applicants respectfully traverse this rejection.

The Examiner asserted that "[t]he scope of this claim includes an enormous number of methods using an enormous number of potential vaccinia viral genomes produced by an unspecified number of methods e.g., homologous recombination, direct ligation, etc."[1] (Office Action at page 8.) The Examiner also asserted that "[a]lthough the specification discloses examples of 'tri-molecular recombination' . . . the specification and claims do not provide **any** examples for other processes like direct ligation and homologous recombination that would likewise yield a 'library' of antibodies upon expression," and that "Applicants have not provided a 'representative' number of examples to show that they were in possession of the full scope of the claims." *Id.* (emphasis in original). Furthermore, the Examiner asserted that "the prior art teaches that only poxvirus vectors that possess genomes capable of undergoing trimolecular recombination . . . will reliably produce recombinants at an efficiency that is amenable for polynucleotide library construction." *Id.* at 10.

The Examiner further asserts that the specification teaches that "libraries of polynucleotides that encode potential antigen-specific human immunoglobulins generally cannot be produced using "traditional' methods of homologous recombination with

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[1] Applicants understand the Examiner's statement to refer to populations of viral genomes produced by different methods, as opposed to individual viral genomes produced by the same method. If this is not a correct interpretation of the Examiner's statement, Applicants respectfully request further clarification.

poxviruses like vaccinia," and that 'direct ligation' was [also] shown to be unsatisfactory ... ." (Office Action at pages 9-10). Applicants respectfully disagree with these assertions as they apply to the claims as amended.

First, Applicants respectfully remind the Examiner that that the written description requirement is met if one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention in the specification as filed. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. §2163.02. The Examiner cited *University of California v. Eli Lilly and Co.* 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997) for the proposition that adequate disclosure requires a ***representative number of examples***. (*See* Office Action at page 8.) However, Applicants respectfully submit that this is an inappropriate characterization of *Eli Lilly*. There is no discussion in *Eli Lilly* that, in order to meet the requirements for adequate disclosure under the patent laws, an applicant must provide a representative number of ***examples***. Rather, the Federal Circuit in *Eli Lilly* set forth several possible tests for determining whether a claimed genus is adequately described, one of which was the "representative number of ***species***" test. *See Eli Lilly* at 1406. Moreover, the Federal Circuit and the PTO have acknowledged that a specification may adequately describe a genus even though it fails to describe a single species falling within the genus. *Eli Lilly* at 1406; M.P.E.P. 2163 (II)(A)(3)(a)(ii) at 2100-169.

Given the disclosure in the present specification, Applicants respectfully submit that the claims are not overly broad, and that one of ordinary skill could reasonably conclude that the inventors had possession of the claimed methods in the specification as filed. Nevertheless, in an effort to facilitate prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 84 to recite that the first and

second libraries are not constructed by traditional homologous recombination. However, Applicants respectfully point out that the Examiner has mischaracterized the specification with respect to the use of other library construction methods, e.g., direct ligation. While the specification does indicate that direct ligation results in a relatively low recombination efficiency and titer (*see* Specification at paragraphs [0022] and [0170]), it does not say that methods such as direct ligation or modified homologous recombination cannot be used to generate vaccinia virus expression libraries, as suggested by the Examiner. Furthermore, while these methods may not be as efficient as tri-molecular recombination, there is no requirement in the claims for a particular titer or recombination efficiency. Thus, contrary to the Examiner's insertion of such a statement into a quotation from the specification, the specification does not say that "only vaccinia virus vectors that are amendable [sic] to 'tri-molecular' recombination will work." (See Office Action at page 13.)

With respect to the Examiner's assertion that "the specification and claims do not provide **any** examples for other processes like direct ligation and homologous recombination," (Office action at page 8) (emphasis in original), Applicants respectfully submit as set forth above, that there is no requirement for a representative number of examples to support an adequate written description. Furthermore, the use of direct ligation and homologous recombination to insert a heterologous genetic element into a vector were known in the art, as evidenced by paragraphs [0019]-[0022] of the specification. As such, they need not be described in the specification. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94 (holding that the description need only describe what is new or non-conventional); M.P.E.P §2163, p. 2100-171, col. 1 (Rev. 2, May 2004). Also, even though not required, the specification

does provide an example of modified homologous recombination. Example 5 describes the use of *modified* homologous recombination to produce recombinant vaccinia viruses, and shows that the method has a 35-fold improvement in frequency of viral recombinants over traditional homologous recombination. (Specification at paragraphs [0318]-[0322]). As such, the specification as filed provides a representative number of species of methods for constructing vaccinia virus libraries.

Given the disclosure in the present case, one of ordinary skill in the art could reasonably conclude that the inventors had possession of the claimed methods when the application was filed. Accordingly, the claimed invention is adequately described, and Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. § 112--Enablement

Claims 84, 88-97, 99, 103, 107-122, and 127-131 were rejected under 35 U.S.C. § 112, first paragraph, because, the specification allegedly does not enable a person skilled in the art to which it pertains to make and use the invention commensurate with the scope of the claims. (Office Action at page 11.) Applicants respectfully traverse this rejection.

The test of enablement is whether one of ordinary skill in the art, given the disclosure at the time of filing, could make and use the claimed invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Examiner addressed several of the "*Wands*" factors to be considered when determining whether experimentation is "undue." *See id.*; (Office Action at pages 11-12). As stated in *Wands*, "'[t]he key word is "undue," not "experimentation."'" *Wands* at 737 (quoting *In re Angstadt*, 537 F.2d at 504, 190 USPQ at 219).

A) Breadth of the claims and nature of the invention

With respect to the breadth of the claims and the nature of the invention, the Examiner argued that:

> The claims are drawn to a broad genus. The scope of these claims include an enormous number of methods using an enormous number of potential viral genomes produced by an unspecified number of methods. Consequently, the nature of the invention cannot be fully determined.[2]

(Office Action at page 12). Applicants respectfully disagree with the Examiner's argument. The Examiner has basically repeated the assertions made with respect to written description. With respect to the number of potential viral genomes mentioned by the Examiner, Applicants respectfully assert that the purpose of an expression library as in the present invention is to generate a potentially large number of vectors that do not have to be individually characterized because the library will be subjected to a selection method to identify the vector containing the insert of interest, a point of which one of ordinary skill in the art would have been aware. The Examiner is further reminded that claim 84 does not require expression of an enormous number of different immunoglobulins, but rather requires expression of a "plurality" of different immunoglobulins, *i.e.*, two or more different immunoglobulins.[3] As discussed in detail above with respect to written description, Applicants have provided disclosure that teaches several methods to construct a library in vaccinia virus vectors and teaches how

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[2] *See* footnote 1, *supra*.

[3] The Federal Circuit has recently held that, in the absence of an alternative meaning in the specification, the term "plurality" includes everything from "more than one" to "a large quantity." *See Bilstad v. Wakalopulos*, 386 F.3d 1116, 1123 (Fed. Cir. 2004). The present specification does not assume an alternate meaning for the term.

to select a vector containing the insert of interest. Therefore, Applicants respectfully submit that the nature of the invention can be fully determined.

B) State of the prior art and level of predictability in the art

With respect to the state of the prior art and level of predictability in the art, the Examiner repeated the incorrect assertion that "only vaccinia virus vectors that are amendable [sic] to 'tri-molecular' recombination will work." (Office Action at page 13.) Applicants respectfully disagree with this assertion. As discussed *supra* with respect to written description, although methods such as direct ligation and modified homologous recombination may be less efficient than tri-molecular recombination for constructing a library in vaccinia virus, the specification does not say that they cannot be used. As stated above, direct ligation was known in the art, and Example 5 in the present specification describes the use of modified homologous recombination for making recombinant vaccinia virus.

The Examiner also stated that "the prior art indicates that vaccinia virus will not infect mammalian host cells without a helper virus," and alleged that "Applicants' method **will not work** without the use of a helper virus." (Office Action at pages 13-14) (emphasis in original). As such, the Examiner alleges that the claims lack critical or essential subject matter. *Id.* Applicants respectfully disagree with the Examiner's allegations. First, Applicants respectfully assert that the specification does not state that *vaccinia virus* is not infectious, as suggested by the Examiner. Rather, the specification states that "*Naked vaccinia virus DNA* is not infectious because the virus cannot utilize cellular transcriptional machinery and relies on its own proteins for the synthesis of viral RNA." (Specification at page 7, paragraph [0018]) (emphasis added). Second, with

respect to viral *nucleic acids* that are not infectious, Applicants point to page 37, paragraph [0109] of the specification as filed, which provides several examples of ways to produce viable progeny virus particles:

> It is noted, however, that certain virus nucleic acids, for example, poxvirus nucleic acids, are not infectious, and therefore must be introduced with additional elements provided, *for example, by a virus particle enclosing the viral nucleic acid, by a cell which has been engineered to produce required viral elements, or by a helper virus.*

Id. (emphasis added). Therefore, contrary to the Examiner's assertions, the state of the art and level of predictability in the art do not support the conclusion that methods other than tri-molecular recombination could not be used to produce vaccinia virus vectors, or that the present invention will not work without a helper virus.

C) Amount of direction provided by inventor and existence of working examples

With respect to the amount of direction provided by the inventor and the existence of working examples, the Examiner asserted that

> Applicants disclose the use of examples that contain "two" non-overlapping fragments of the v7.5/tk virus genome produced using the NotI and ApaI restriction enzymes and "one" recombinant plasmid containing TLK/TKR and the library of human immunoglobulin genes to produce the vaccinia virus vectors. In addition, all examples employ the use of a "helper" virus like fowlpox virus.

(Office Action at page 14.) Applicants respectfully remind the Examiner that "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." M.P.E.P. § 2164.02 at 2100-187 (citing *In re Borkowski*, 422 F.2d 904, 908, 164 U.S.P.Q. 642, 645 (CCPA 1970)). Furthermore, in the present case, as acknowledged by the Examiner, Applicants do provide examples, even though they are

not required. However, the disclosure is not limited to the examples. "How a teaching is set forth, by specific example or broad terminology, is not important." M.P.E.P. § 2164.08 at 2100-198 (citing *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 370 (CCPA 1971)). As set forth, *supra*, the present specification provides extensive disclosure on how to make and use vectors, including vaccinia virus vectors (*see, e.g.*, Specification at pages 48-63, paragraphs [0131]-[0169]; pages 63-76, paragraphs [0170]-[0205] (tri-molecular recombination)). There is also disclosure in the specification as filed on a variety of ways to introduce viral nucleic acids into host cells (see Specification at page 37, paragraph [0109]. Thus, there is ample direction provided in the present specification, some in the form of examples .

D) Quantity of experimentation needed to make or use invention

With respect to the quantity of experimentation needed to make or use the invention based on the content of the disclosure, the Examiner asserted that:

> As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and[/]or use the invention would be great.

(Office Action at page 14.) Applicants respectfully disagree with the Examiner's assertions.

First, the fact that some experimentation may be required does not preclude enablement, so long as the experimentation is not undue. *Wands*, 858 F.2d at 736-737. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should

proceed." *Id.* at 737. Second, contrary to the Examiner's assertions, as stated above, the specification does provide specific guidance to practice the invention, including, but not limited to, guidance regarding immunoglobulins (*see, e.g.,* Specification at paragraphs [0057]-[0105]), antigens (*see, e.g.,* Specification at paragraphs [0113]-[0119]), signal peptides (*see, e.g.,* Specification at paragraphs [0096]-[0105]), transcriptional control regions (*see, e.g.,* Specification at paragraphs [0079]-[0081]), vectors (*see, e.g.,* Specification at paragraphs [0131]-[0169]),and selection and screening strategies for isolating recombinant immunoglobulin molecules (*see, e.g.,* Specification at paragraphs [0206]-[0269]), as well as methods of constructing libraries using modified homologous recombination, direct ligation, and tri-molecular recombination (*see, e.g.,* Specification at paragraphs [0170]-[0205]). In addition, the specification provides illustrative, non-limiting examples of specific embodiments of the present invention (*see, e.g.,* Specification at paragraphs [0275]-[0414]).

The Examiner further asserted that "Applicants have not provided any working examples that would teach this enormous genus that falls within a highly unpredictable art area." (Office Action at page 14.) Applicants respectfully disagree with the Examiner's assertions. Working examples are not required in order to comply with the enablement requirement of 35 U.S.C. § 112, 1st paragraph. *See, e.g.*, M.P.E.P. § 2164.02. As the Examiner, himself, stated, "there must be sufficient disclosure, *either through illustrative examples or terminology*, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed." (Office Action at page 14) (citing *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 U.S.P.Q.2d 1438, 1445 & n.23 (Fed. Cir. 1991) (emphasis added). In the present case, as detailed above with specific references to the specification as filed, Applicants have provided examples and

terminology sufficient to teach one of ordinary skill in the art to practice the methods of the present invention.

The analysis of the various factors for determining whether the experimentation required to practice the claimed invention would be undue, clearly shows that it would not be. Namely, the claims are not overly broad in light of the extensive disclosure of the various aspects of the invention. Moreover, the state of the art and level of predictability in the art at the time of filing were such that, given the disclosure, one of ordinary skill in the art could practice the invention. Furthermore, one of ordinary skill in the art, given the specification, could make and use the invention without undue experimentation because there is ample direction provided in the specification, and there are examples to illustrate various aspects of the present invention. The weighing of these factors indicates that the claims are enabled. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 103

Claims 84, 88-97, 99, 103, 107-122, and 127-131 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rowlands *et al.*, WO 93/01296 (hereinafter "Rowlands"), Zauderer, WO 00/28016 (hereinafter "Zauderer"), and Waterhouse *et al.*, *Nuc. Acids Res.* 21: 2265-66 (1993) (hereinafter "Waterhouse"). (Office Action dated September 7, 2004, Page 16, Section 22.) Applicants respectfully traverse this rejection.

In particular, the Examiner asserted that:

> It would have been obvious to one skilled in the art at the time the invention was made to make a library of vaccinia virus vectors as taught by Zauderer et al. to express fully functional antibodies as taught by

> Rowlands et al. for the purpose of screening and/or affinity maturation as taught by Waterhouse et al. because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.) and Waterhouse et al. teach that such a library would be useful in screening and affinity maturation. Applicants respectfully disagree with these assertions.

Section 2143 of the M.P.E.P. sets forth the basic requirements for a *prima facie* showing of obviousness:

> First, there must be some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference. . . must teach or suggest all the claim limitations.

The M.P.E.P further states that "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." *Id.* Applicants respectfully assert that the Examiner has not met these requirements to establish a *prima facie* case of obviousness.

First, the Examiner has not shown that there was some suggestion or motivation to combine Rowlands, Zauderer, and Waterhouse to arrive at the claimed invention. The Examiner contended that:

> . . . one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the [sic] their "tri-molecular" approach represents and easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. . . . In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" . . ., which would encompass the "associated" heavy/light chains described by Rowlands et al.

(Office Action at pages 21-22) (citations omitted). Applicants respectfully disagree with this contention and remind the Examiner that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the *desirability* of the combination." M.P.E.P. § 2143.01, p. 2100-131, 1st column (Rev. 2, May 2004) (citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) (underline in original) (italics added).

In the present case, the Examiner has pointed to nothing specific in Rowlands, Zauderer, or Waterhouse that would have motivated or suggested to one of ordinary skill in the art the desirability of combining these references. While Rowlands describes the expression of a single, recombinant antibody using a vaccinia virus vector, there is no suggestion provided therein that would have motivated one of ordinary skill in the art to construct first and second libraries of polynucleotides in vaccinia virus vectors. Furthermore, while Zauderer describes the use of vaccinia virus vectors for the generation of libraries expressing tumor, cancer, or infected cell-specific antigens, there is no suggestion to one of ordinary skill in the art to introduce into a population of mammalian host cells first and second vaccinia virus expression libraries encoding immunoglobulins as in the present invention. Finally, Waterhouse does not even describe vaccinia virus vectors or mammalian host cells; rather, Waterhouse describes the generation of large phage antibody repertoires and subsequent infection into bacterial hosts for phage display. Hence, there is absolutely nothing in Waterhouse to suggest to one of ordinary skill in the art to construct vaccinia virus expression libraries encoding human immunoglobulin subunit polypeptides for use in selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule or an antigen-specific fragment thereof as in the present invention. In fact, Waterhouse describes how to

improve phage display, a method that requires bacterial hosts and a bacteriophage vector. Clearly, one of ordinary skill in the art would not have been motivated to combine Waterhouse with a method using an animal virus vector such as vaccinia virus to create expression libraries in *mammalian* host cells. The Examiner also has not pointed to any acceptable objective evidence or sound scientific reasoning that would provide a motivation to combine Rowlands, Zauderer, and Waterhouse. The Examiner is reminded that there is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of the invention. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Since there is no suggestion or motivation to combine Rowlands, Zauderer, and Waterhouse, they cannot properly be combined to render the claimed invention obvious.

Second, one of ordinary skill in the art would not have had a reasonable expectation of success combining Rowlands, Zauderer, and Waterhouse to arrived at the present invention. The Examiner contends that "Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and Waterhouse et al. teach several successful examples of associated light/heavy chains that can be used for screening and/or antibody maturation, which would encompass the heavy/light chain antibodies disclosed by Rowlands et al." (Office Action at page 22.) Applicants respectfully disagree with the Examiner's contentions.

In particular, one of ordinary skill in the art would not have reasonably expected that the phage display technology described in Waterhouse could be extrapolated to methods of generating expression libraries of polynucleotides constructed in an animal virus like vaccinia and introduced into mammalian host cells as in the present invention. As stated above, Waterhouse describes the generation of a phage library, which involves

the use of filamentous bacteriophage as a vector, and bacterial cells as hosts. In contrast, vaccinia is an animal virus and is introduced into mammalian host cells for expression. Given these different vectors and host cells, one of ordinary skill in the art would not have expected any screening methods described in Waterhouse to be useable with vaccinia virus vectors because there would be different conditions required for the two systems. In fact, the present specification distinguished phage display methods because it suffers from many drawbacks as compared to the present invention (See Specification, paragraph [0008]) ("Since phage display methods normally only result in the expression of an antigen-binding fragment of an immunoglobulin molecule, after phage selection, the immunoglobulin coding regions from the phage must be isolated to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host including mammalian cells, insect cells, plant cells, yeast, and bacteria.")) Neither Rowlands nor Zauderer would have provided the skilled artisan with a reasonable expectation of success because Rowlands does not describe using libraries of vaccinia virus vectors (*i.e.*, Rowlands describes *a* recombinant antibody in a vaccinia virus vector), and Zauderer does not describe screening first and second vaccinia virus expression libraries encoding immunoglobulins. Therefore, absent a reasonable expectation of success, the cited references cannot properly be combined to render the claimed invention obvious.

Since there was no suggestion or motivation to combine Rowlands, Zauderer, or Waterhouse, and no reasonable expectation of success from the combination, the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection Based on Non-Statutory Obviousness-Type Double Patenting

In the Office Action at pages 23-24, the Examiner has provisionally rejected claims 84, 88-97, 99, 103, 107-122, and 127-131, for alleged obviousness-type double patenting over claims 1-84 of commonly-owned U.S. Patent Application Publication No. 2003/0104402 A1 ("the '402 publication") in view of Rowlands. Applicants respectfully traverse this rejection, and contend that claims 84, 88-97, 99, 103, 107-122, and 127-131 would not have been obvious to one of ordinary skill in the art over claims 1-84 of the '402 Publication in view of Rowlands.

One of ordinary skill in the art would not have had a reasonable expectation of success in combining Rowlands with the '402 publication to arrive at the present invention. Rowlands describes the use of vaccinia virus vectors for making an *individual* recombinant antibody, not an immunoglobulin expression library. There would have been no indication to one of ordinary skill in the art that the methods for making or screening a library of intracellularly expressed immunoglobulins, as described in the '402 publication could be used to make or screen a library of extracellularly expressed immunoglobulins as in the present invention based on the disclosure in Rowlands of an individual antibody that is expressed extracellularly, as described in Rowlands. Reconsideration and withdrawal of the rejection therefore are respectfully requested.

However, if the Examiner is not inclined to withdraw the rejection, then Applicants respectfully request that it be held in abeyance until such time as otherwise patentable subject matter has been identified in either the present application or the '402 publication. At that time, Applicants will consider filing a terminal disclaimer to obviate the double-patenting rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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